REMARKS

Claims 12-14, 16-18, 31, and 33-38 are pending in the application. Applicants respectfully request entry of this Amendment and reconsideration of the outstanding objections and rejections in this application.

Applicants have received and reviewed an Office Action dated November 19, 2002. By way of response, Applicants have cancelled claims 31 and 33 without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in a continuation application. Applicants have amended claim 14. The amendment to claim 14 is supported throughout the specification including at page 48, line 1 to page 52, line 21. No new matter is presented.

Applicants have presented new claims 39-47. The new claims are supported throughout the specification including at page 13, lines 8-24; page 22, line 11 to page 23, line 20; page 28, line 11 to page 12, line 20; and page 97, line 14 to page 98, line 7. Applicants submit that the newly presented claims do not raise any issues of new matter.

Filing Receipt

Applicants note that they still have not received a filing receipt for this application. Applicants have previously requested the filing receipt in a communication dated March 28, 2002. Applicants request that the Examiner provide us with a filing receipt as soon as possible.

35 U.S.C. § 112, Second Paragraph

U.S.C. § 112, second paragraph.

35 U.S.C. § 112, First Paragraph

Enablement

Claims 12-14, 16-18, 31, and 33-38 stand rejected under 35 U.S.C. § 112, first paragraph on the grounds that the specification is not enabling for the full scope of the claimed invention. The Examiner contends that the specification, inter alia, fails to teach how to make bispecific antibodies and only teaches how to screen a scFv library to identify light chains that bind to two different heavy chains to make binding domains that bind to different antigens. The Examiner also contends that a specific example of a bispecific antibody with specificity for Her-3 and Ob-R does not appear to have a utility that is specific and substantial. Applicants have cancelled claims 31 and 33 rendering the rejection of these claims moot. Applicants respectfully traverse this rejection with respect to claims 12-14, 16-18 and 34-38.

Applicants' claims are directed to a bispecific antibody comprising two polypeptides each comprising a heavy chain, a light chain, and a multimerization domain, wherein the light chains have at least 80% sequence identity, and the first and second polypeptides dimerize by interaction of the first and second multimerization domains.

Applicants contend that one of skill in the art reading the specification would be able to prepare the claimed bispecific antibodies without undue experimentation. There are many factors to be considered in an analysis of enablement, including the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill,

citing in re Wands, 858 F 2d. 731,737 (Fed. Cir. 1988). Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims.

Applicants submit that one of skill in the art reading the specification would be able to make the bispecific antibodies as claimed. Applicants have provided a detailed description of making the starting materials, generating multimerization domains and expressing or producing bispecific antibodies. Contrary to the Examiner's assertion, Applicants have provided working examples of two different bispecific antibodies: anti-Ob-R/ anti-HER3 and anti-Mpl/anti-HER3. In Example 4, Applicants describe identification of antibodies that share a common light chain. See pages 96 to 98, line 7. In Figure 4, Applicants describe the sequences of the light chain of 8 different antibodies. In Example 4, Applicants also describe the preparation of anti-Ob-R and anti-HER3 to form a bispecific antibody using clones having a common light chain sequence at page 99, line 21 to page 101, line 18 and page 102, line 16 to page 103, line 4. Example 4 also provides a working example of anti-Mpl/anti-HER3 bispecific antibody (see pages 104, line 25 to page 106, line 24). This bispecific antibody was assessed for binding to both antigens using ELISA.

Thus, Applicants submit that Applicants have described how to make bispecific antibodies in the specification and have provided working examples of the preparation of 2 different bispecific antibodies having common light chains: anti-Ob-R/anti-HER3 and anti-Mpl/anti-HER3. In addition, Applicants have provided many different examples of

[illegible] Applicants submit that the specification provides sufficient direction

and working examples that would allow one of skill in the art to prepare a bispecific antibody as claimed without undue experimentation.

The Examiner also alleged that minor modifications in the binding domain of antibodies can drastically change its binding ability. The Examiner stated that the specification failed to teach examples wherein the common light chain sequences were not identical, yet retained the ability to pair with either heavy chain and the ability of the resulting binding domains to bind antigen. The Examiner concluded that the art of antibody engineering is highly unpredictable such that one of skill in the art would not have a reasonable expectation for success in how to make the full scope of the claimed antibodies.

Applicants submit that it is well settled that the specification need not disclose every species encompassed by the claims, even in an unpredictable art. *See* In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). Rather, in the biotechnological arts, the disclosure must adequately guide one of skill in the art to determine, without undue experimentation, which species encompassed by the claimed genus possess the disclosed utility. *Id.* Applicants also respectfully submit that the citation by the Examiner to the Rudikoff et al. reference concerning unpredictability of antibody engineering is not relevant for evaluating the enablement of this application because Rudikoff et al was published in 1982 and this application claims to priority to May 1997, some 15 years later, during which time the level of knowledge and predictability in the biotechnology and antibody

encompassed by the claims based on Applicants' disclosure coupled with the skill of

the relevant arts.

As stated above, the present application discloses several common light chains suitable for use in the present invention whose amino acid sequence identities are not identical. See Figure 4. Applicants have also described a method for identifying common light chain sequences between antibodies of different specificities. (See, for example, Example 4, page 96, line 1 to page 98, line 7). Applicants further disclose that in some embodiments, the light chains differed in sequence identity only in residues located outside of the antigen binding domains (page 97, lines 27-30). Furthermore, Applicants have disclosed a method of testing the binding specificity of the antibodies of the invention (page 101, line 19 to page 102, lines 15). It would be routine experimentation for one of skill in the art using the methods as described in the invention to determine if the bispecific antibody with a common light chain would bind to both of the antigens. Some experimentation, even considerable experimentation is permissible if it is routine. Therefore, Applicants respectfully submit that the present disclosure provides substantial guidance in ascertaining species in the claimed genus, for at least these reasons.

Finally, the Examiner stated that one of skill in the art would not know how to use the Her-3/Ob-R bispecific antibody disclosed in the Examples, as it does not have an asserted utility that is specific and substantial. Applicants have cancelled claim 31 rendering the rejection of this claim on this basis moot.

Applicants submit they have described a number of uses of bispecific antibodies including therapeutic uses, diagnostic uses, enzyme immunoassays, and to determine the

specification. Applicants submit, therefore, that the disclosure more than adequately enables one of skill in the art to make and use the heteromultimers of the claims.

Withdrawal of this rejection is respectfully requested.

Written Description

The Examiner also rejected claims 12-14, 16-18, 31, and 33-38 under 35 U.S.C. § 112, first paragraph on the grounds that Applicants were not in possession of the claimed inventions at the time of filing, because the disclosure fails to adequately describe the claimed genus of compounds. Applicants respectfully traverse this rejection.

Applicants remind the Examiner that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *See* Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph "Written Description Requirement" IIA. The determination of whether a specification meets the written description requirement depends upon several factors, including:

a) partial structure;

b) physical and/or chemical properties;

c) functional characteristics;

d) known or disclosed correlation between structure and function;

e) method of making.

Applicants respectfully submit that when the above factors are carefully weighed, the specification describes the claimed subject matter in such a way as to reasonably convey

[illegible] stated that the disclosure of multiple examples [illegible]

have common light chains but different antigen specificities is not representative of the

claimed genus, which includes scFv pairs that bind any antigen and wherein the light chains are not identical but closely related. The Examiner claimed that while the specification generally contemplates such scFv pairs, it does not describe such pairs structurally or give specific directions for making them.

Regarding the scope of the genus as including scFv pairs that bind to any antigen, Applicants submit that the application describes the genus in a manner that clearly demonstrates Applicants were in possession of the claimed invention. Applicants have disclosed the panning of a large human scFv antibody library for antibodies specific for eleven different antigens that represent considerable variation in structure and function (page 96, lines 1-13). After comparing the V_L sequences of the antibodies, Applicants discovered at least one, and often more than one, common light chain for most pairwise comparisons (page 96, lines 25-26). Based upon these results, it is likely that common light chains can be found for any V_L comparison. Thus, Applicants have not only described multiple scFv pairs within the claimed genus, but have produced evidence that Applicants' methods are applicable to identifying a common light chain of an antibody for any number of different antigens.

Applicants have also provided detailed working examples for the identification, preparation, and isolation of the different bispecific antibodies having common light chains in Example 4. Applicants have also provided in Example 4 structural and functional characteristics of these scFv pairs. Applicants have characterized the

[illegible] by their binding specificity [illegible] standard [illegible] procedures.

Regarding the scope of the claims including bispecific antibodies comprising light chains that are closely related but not identical, Applicants disclose multiple examples of light chains suitable for use in preparation of the heteromultimers of the invention that are not identical, but are closely related (page 97, line 14 to page 98, line 7). The sequences of these chains, furthermore, are disclosed in Figure 4.

Therefore, Applicants submit that the specification describes physical and/or chemical properties, structural and functional characteristics, and methods of making or isolating the antibodies of the invention. When all of these factors are weighed, Applicants respectfully submit that one of skill in the art would recognize that Applicants had possession of the claimed invention. Based on the above, Applicants request withdrawal of the rejection.

35 U.S.C. § 112, Second Paragraph

The Examiner rejected claim 14 under 35 U.S.C. § 112, second paragraph. The Examiner indicated that the phrase "the original nucleic acid" lacks antecedent basis in claim 13. Applicants have amended claim 14 to clarify the subject matter of claim 14 and respectfully request withdrawal of the rejection of the claim.

35 U.S.C. § 103

The Examiner rejected claims 12-14, 16-18 and 34-38 as unpatentable over

[illegible] No. 5,807,706) or Carter (WO 96 27011). The Examiner contends that it would be prima

facie obvious to one of ordinary skill in the art to engineer a bispecific antibody as described in Bosslett using the common light chains as described in Vaughan in combination with the multimerization regions as taught by either Ridgeway, Carter or Carter. Applicants respectfully traverse the rejection.

As an initial matter, Applicants submit that the Carter et al patent, Patent No. 5,807,706, is not properly considered prior art under 35 U. S. C. 103 (a). The Carter et al. reference is a U.S. patent with a filing date of March 1, 1995 and an issue date of September 15, 1998. It appears that the Examiner has considered this reference prior art under § 102(e). The rejection notes the filing date of the Carter et al. reference. Further, this reference qualifies as prior art only under § 102(e).

A reference that is prior art only under § 102(e) cannot be used, according to § 103(c), in an obviousness rejection if the subject matter of the cited reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. A clear statement of entitlement to the prior art exclusion by Applicants or a registered practitioner is a sufficient evidence to establish the prior art exclusion (Examination Guidelines for 35 U.S.C. § 102(e) (as amended and revised) at IV(5); 1266 TMOG 80, January 14, 2003).

Applicants hereby make a clear statement of entitlement to exclude the Carter et al. reference as prior art as provided by § 103(c). The Carter et al. patent is assigned to the assignee of the present patent application. The Carter et al. patent and the present

subject to an obligation of assignment to the same person

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) suggestion or motivation to, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; and 3) a reasonable expectation of success. Applicants submit that all of these requirements have not been met because, in the least, there is no motivation to combine or modify the references to obtain the claimed invention.

The Vaughan et al. reference discloses and is directed to a scFv phage library of naïve antibody variable domains. The reference reports that the same light chain is sometimes paired with different heavy chains in antibodies with different specificities. However, this reference does not teach or suggest that such light chains should be selected over other light chains or that these light chains can or should be used in bispecific antibodies. In addition, Vaughan et al. does not describe the use of multimerization domains.

The deficiency of the Vaughan et al. reference is not remedied by reference to Bosslet et al. The Bosslet et al. reference is directed to bispecific and oligospecific mono and oligovalent receptors. This reference describes the fusion of F(ab) fragments of antibodies of different specificities by means of linkers. The Bosslet et al. reference does not teach or suggest formation of bispecific and oligospecific receptors with a common

multimerization region or a polypeptide to form a bispecific or oligospecific receptor

The Carter et al. reference (WO 96/27011) and the Ridgeway et al. reference are directed to forming heteromultimers with a multimerization region. These references do not teach or suggest a heteromultimer with a common light chain. The Ridgeway reference is directed to an antibody/ immunoadhesin bispecific molecule and common light chains are not found in this type of bispecific molecule. The Carter et al reference is directed to forming a multimerization domain and does not teach or suggest a common light chain for a bispecific antibody.

Therefore, Applicants submit that one of skill in the art would not be motivated to combine or modify the references as cited by the Examiner. The Vaughan et al. reference describes the occurrence of the same light chain in scFvs of different specificities in a phage display library but does not teach or suggest the selection of a common light chain over other light chains for use in a bispecific antibody. The Bosslet reference also does not describe using a common light chain in an oligospecific receptor but rather is directed to fusing F(ab)s of two different specificities. Finally, the Carter et al. and Ridgeway references concern the formation of heteromultimers using a multimerization region and also do not describe using a common light chain. Therefore, one of skill in the art would not be motivated to combine or modify these references to achieve Applicants' claimed invention.

Applicants respectfully submit the Examiner is improperly using hindsight reconstruction. As the Federal Circuit stated in In re Fine "we cannot use hindsight

re Fine case, the examiner is picking and choosing isolated disclosures and has not established a suggestion, teaching or motivation to combine these references.

Thus, Applicants respectfully request withdrawal of the 35 U.S.C. §103 rejection of these claims.

Summary

Applicants submit that all pending claims are in condition for allowance, and notice to that effect is earnestly requested. The Examiner is invited to contact Applicants' representative at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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Dated: March 14, 2003

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MARKED UP VERSION OF THE CLAIMS

14. (Amended) The bispecific antibody of claim 13, wherein the [nucleic acid encoding the first polypeptide or the nucleic acid encoding the second polypeptide, or both, has] first polypeptide is encoded by a first nucleic acid and the second polypeptide is encoded by a second nucleic acid, wherein the first or second nucleic acid or both have been altered from the original nucleic acid to encode the multimerization domain or a portion thereof.

Set of Claims After Entry of Amendment

12. A bispecific antibody prepared by the method comprising:

(a) expressing in a host cell a first polypeptide comprising a first heavy chain variable domain, a first or second light chain variable domain, and a first multimerization domain, wherein the first and second light chain variable domains have at least 80% amino acid sequence identity, and wherein a first binding domain is formed by the first heavy chain variable domain and the first or second light chain variable domain;

(b) expressing in the host cell a second polypeptide comprising a second heavy chain variable domain, the first or the second light chain variable domain, and a second multimerization domain, wherein a second binding domain is formed by the second heavy chain variable domain and the first or second light chain variable domain, and wherein the first and second binding domains bind different antigens;

(c) allowing the first and second polypeptides to dimerize by interaction of the first and second multimerization domains to form a bispecific antibody; and

(d) recovering the bispecific antibody from the host cell.

13. A bispecific antibody comprising a first polypeptide and a second polypeptide, the bispecific antibody comprising:

(a) the first polypeptide which comprises a first heavy chain variable domain, a first or second light chain variable domain, and a first multimerization domain, wherein the first and second light chain variable domains have at least 80% amino acid sequence

identity and the first or second light chain variable domain;

(b) the second polypeptide which comprises a second heavy chain variable domain, the first or the second light chain variable domain, and a second multimerization domain, wherein a second binding domain is formed by the second heavy chain variable domain and the first or second light chain variable domain, and wherein the first and second binding domains bind different antigens;

(c) the first and second polypeptides dimerize by interaction of the first and second multimerization domains to form a bispecific antibody.

14. The bispecific antibody of claim 13, wherein the first polypeptide is encoded by a first nucleic acid and the second polypeptide is encoded by a second nucleic acid, wherein the first or second nucleic acid or both have been altered from the original nucleic acid to encode the multimerization domain or a portion thereof.

16. The bispecific antibody of claim 14, wherein the multimerization domains of the first and second polypeptide interact at an amino acid side chain protuberance of one of the first and second polypeptides and an amino acid side chain cavity of the other polypeptide.

17. The bispecific antibody of claim 16 wherein at least one of the protuberance and cavity is generated by an alteration in which a naturally occurring amino acid is imported into the first or second polypeptide.

18. A composition comprising the bispecific antibody of claim 13 and a carrier.

34. The bispecific antibody of claim 13, wherein the first and second light chain

35. The bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 95% amino acid sequence identity

36. The bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 98% amino acid sequence identity.

37. The bispecific antibody of claim 13, wherein the first ands second light chain variable domains have at least 99% amino acid sequence identity.

38. The bispecific antibody of claim 13, wherein the first and second light chain variable domains have identical amino acid sequences.

39. A bispecific antibody prepared by the method comprising:

(a) expressing in a host cell a first polypeptide comprising a first heavy chain variable domain, a first or second light chain variable domain, wherein the first and second light chain variable domains have at least 80% amino acid sequence identity, and wherein a first binding domain is formed by the first heavy chain variable domain and the first or second light chain variable domain;

(b) expressing in the host cell a second polypeptide comprising a second heavy chain variable domain, the first or the second light chain variable domain, wherein a second binding domain is formed by the second heavy chain variable domain and the first or second light chain variable domain, and wherein the first and second binding domains bind different antigens;

(c) allowing the first and second polypeptides to dimerize to form a bispecific antibody; and

(d) recovering the bispecific antibody from the host cell.

40. A bispecific antibody comprising a first polypeptide and a second polypeptide, the bispecific antibody comprising:

first and second light chain variable domains, wherein the first and second light chain variable domains have at least 80% amino acid sequence identity, and wherein a first

binding domain is formed by the first heavy chain variable domain and the first or second light chain variable domain;

(b) the second polypeptide which comprises a second heavy chain variable domain, the first or the second light chain variable domain, wherein a second binding domain is formed by the second heavy chain variable domain and the first or second light chain variable domain, and wherein the first and second binding domains bind different antigens; and

(c) the first and second polypeptides dimerize to form a bispecific antibody.

41. A composition comprising the bispecific antibody of claim 40 and a carrier.

42. The bispecific antibody of claim 40, wherein the first and second light chain variable domains have at least 90% amino acid sequence identity.

43. The bispecific antibody of claim 40, wherein the first and second light chain variable domains have at least 95% amino acid sequence identity.

44. The bispecific antibody of claim 40, wherein the first and second light chain variable domains have at least 98% amino acid sequence identity.

45. The bispecific antibody of claim 40, wherein the first ans second light chain variable domains have at least 99% amino acid sequence identity.

46. The bispecific antibody of claim 40, wherein the first and second light chain variable domains have identical amino acid sequences.

47. A bispecific antibody comprising a first polypeptide and a second polypeptide, the

(a) first polypeptide which comprises a first heavy chain variable domain, a first or second light chain variable domain, wherein the first and second light chain variable domains have at least 80% amino acid sequence identity and have at least one

CDR region that has the same sequence, and wherein a first binding domain is formed by the first heavy chain variable domain and the first or second light chain variable domain;

(b) the second polypeptide which comprises a second heavy chain variable domain, the first or the second light chain variable domain, wherein a second binding domain is formed by the second heavy chain variable domain and the first or second light chain variable domain, and wherein the first and second binding domains bind different antigens;

(c) the first and second polypeptides dimerize to form a bispecific antibody.